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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,113	PIZZA ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-19* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed on May 11, 2010 is acknowledged. Claims 1-8 and 11-19 are pending. Claim 12 has been amended. Claims 13-18 were previously withdrawn. Claims 1-8, 11, 12 and 19 are under examination.

Objections Withdrawn

2. In view of Applicant's amendment, the objection to claim 12 because on first sight the acronym "OMV" should be followed by "Outer Membrane Vesicle" is withdrawn.

3. In view of Applicant's amendment to the specification, the objection to the specification because Figure 3 contains sequences that have not been identified by sequence identifiers (i.e. SEQ ID NO) in the drawings or in the Brief Description of the Drawings is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. The rejection of claims 1-3, 5-7, 11 and 12 under 35 U.S.C. 102(e) as being anticipated by Gorringe et al. (WO 01/73080 A2) is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) Gorringe fails to teach an "outer membrane vesicle preparation from a bacterium, wherein….and the bacterium is *N. meningitidis* or *N. gonorrhoeae*. The section cited by the Examiner teaches expression of the tbp from a pathogenic Neisseria "in a commensal Neisserial host".

2) Gorringe does not teach the claimed invention because the limitations are not arranged or combined in the same way as recited in the claim.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

With regard to Point 1, contrary to Applicant's assertion, Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA. Gorringe et al. further disclose that the iron uptake proteins expressed according to the invention are derived from

pathogenic Neisseria; and in specific embodiments, transferring binding proteins from Neisseria, specifically *N. meningitidis*, have been expressed (see page 7, lines 16-18).

With regard to claim 1, which recites in part "the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent" and claim 2 recites in part that "the bacterial membrane is disrupted substantially in the absence of any detergent". The requirements of the claims have been meet because while Gorringe et al. disclose that the Tbp is *extracted* by solubilising the membrane associated with Tbp in a non-ionic detergent solution (see page 6, lines 1 and 2); the actual step of disrupting cells was accomplished with a bead-beater followed by adding the cell suspension to a vessel where a detergent is present. In essence, the disruption of the cells is done substantially in the absence of any detergent because no detergent is present during the disrupting aspect of Gorringe et al.

With regard to Point 2, Applicant points out Gorringe use of different embodiments stating that the claims are not anticipated for this reason. Gorringe et al. disclose the method as claimed (see page 5, lines 26 and 35; page 4, lines 4, 5 and 12-14; page 7, lines 16-20; page 6, lines 1 and 2). Applicant points to page 12 to support said argument, however, page 12 is geared toward extraction from whole cells, which would necessarily encompass an outer membrane vesicle. Couple the teachings of page 12 with the teachings that the iron uptake proteins expressed according to the invention are derived from pathogenic Neisseria; and in specific embodiments, transferring binding proteins (tbpA) from Neisseria, specifically *N. meningitidis*, have been expressed (see page 7, lines 16-18) the limitations of said claim have been met.

By Applicant's submission in the remarks on page 12, 2nd line of the second paragraph, Gorringe teaches generation of OMVs. Applicant has not provided any evidence to the contrary, that the process of Gorringe et al. would yield a materially different end result.

As previous presented, Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA (see page 5, lines 26 and 35). Gorringe et al. disclose that the invention provides a cell expressing Neisserial transferring binding protein (Tbp), wherein the Tbp can be extracted from the cell under mild conditions. Gorringe et al. disclose that the invention is an application for the overexpression of Tbps in organisms that are known to express Tbps. The invention is designed to use commensal Neisseria expressing an iron uptake protein from a pathogenic Neisseria, particularly one expressing TbpA, such as *N. meningitidis* strain K454, which is a serogroup B bacterium (see page 4, lines 4, 5 and 12-14; page 7, lines 16-20). Gorringe et al. disclose that the Tbp is extracted by solubilising the membrane associated with Tbp in a non-ionic detergent solution (see page 6, lines 1 and 2), thus meeting the limitation "in the absence of deoxycholate detergent". Moreover, Gorringe et al. disclose that crude membranes were prepared by disrupting cells with a bead-beater (the Examiner has interpreted this to meet the limitation of "wherein the bacterial membrane is disrupted substantially in the absence of any detergent). The cell suspension was transferred to a vessel half filled with 0.25-0.5mm diameter glass beads. The vessel was sealed and placed on to the bead-beating apparatus. The suspension was beaten for 15 seconds to disrupt the cells. Once the beads had settled the suspension was decanted off and centrifuged at 8000g for 30 min. The supernatant was discarded and the pellet containing crude membranes was resuspended in the original volume of 100 mM Tris-HCl buffer, pH 8,0, containing 0.5M NaCl. Once an even suspension was obtained an equal volume of Tris-HCl buffer, pH 8.0, containing 0.5M NaCl and 4% (v/v) Elugent ™ detergent was added. The suspension was incubated with gentle stirring at 4°C for 16 h. The suspension was then centrifuged at 39000g for 10 mi and the supernatant containing soluble rTbps was decanted off (see page 12, lines 25-37 and page 13, lines

1-2; extraction from membrane preparations). Lastly, Gorringe et al. disclose that the composition can be included in vaccine compositions (see abstract).

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of claims 1-8, 11,12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (Analytical Biochemistry, 1994; 216: 47-51) in view of Gorringe et al. (WO 01/73080 A2) as applied to claims 1-3, 5-7, 11 and 12 above, and van der Ley et al. (Vaccine; 1995; 13(4): 401-407) and further in view of Rosenqvist et al. (WO 01/91788 A1) is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) The teachings of Gorringe have been discussed in detail above and only teach generation of OMVs from commensal Neisseria strains.

2) Gorringe does not teach that the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent.

3) Morein, van der Ley and Rosenqvist do not cure the deficiency of Gorringe because neither of them teaches disrupting the bacterial membrane substantially in the absence of deoxycholate detergent.

Applicant's arguments have been considered but are deemed non-persuasive.

The rejected claims are drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

With regard to Point 1, as discussed above, Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA. Gorringe et al. further disclose that the iron uptake proteins expressed according to the invention are derived from pathogenic Neisseria; and in specific embodiments, transferring binding proteins from Neisseria, specifically *N. meningitidis*, have been expressed (see page 7, lines 16-18).

With regard to Point 2, claim 1 recites in part "the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent" and claim 2 recites in part that "the bacterial membrane is disrupted substantially in the absence of any detergent". The requirements of the claims have been meet because while Gorringe et al. disclose that the Tbp is *extracted* by solubilising the membrane associated with Tbp in a non-ionic detergent solution (see page 6, lines 1 and 2); the actual step of

disrupting cells was accomplished with a bead-beater followed by adding the cell suspension to a vessel where a detergent is present. In essence, the disruption of the cells is done substantially in the absence of any detergent because no detergent is present during the disrupting aspect of Gorringe et al.

With regard to Point 3, Morein, van der Ley and Rosenqvist were not used to cure the deficiency of disrupting the bacterial membrane substantially in the absence of deoxycholate detergent. Said limitation had been met by the teachings of Gorringe et al. Morein is the primary reference which taught all the limitations except for specifically teaching that the outer membrane vesicle preparation is from *N. meningitidis* strain H44/76, *N. gonorrhoeae* and over-expresses TbpA; and they do not disclose that the process comprises sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition or that the pore size is about 0.2 μm. van der Ley et al. disclose the use of *Neisseria meningitidis* strain H44/76 (claim 19) for the production of an outer membrane vesicle vaccine. Rosenqvist et al. disclose a process for the production of outer membrane vesicle vaccines. Rosenqvist et al. disclose that sterile filtration of purified OMV is accomplished by using a series of three separate filters with decreasing pore sizes (claim 4) (see page 20, lines 1-12). Moreover, Rosenqvist et al. disclose the use of 0.2 μm filters (claim 8) (see page 20, line 30). The combination of references renders the claimed invention obvious.

As previously presented, Morein et al. disclose a rapid and simple method of preparing outer membrane vesicles from a Gram negative bacterium. The process includes lysing the bacteria to prepare membrane vesicles. Morein et al. disclose that the cells were either passed through a French pressure cell or converted to spheroplast

and briefly sonicated (see page 48; Preparation of Membrane Vesicles; 1st paragraph). Morein et al. disclose that after lysis of the bacteria, unlysed cells were sedimented by a low-speed centrifugation at $1500g_{max}$ for 15 minutes. The membrane vesicles from the supernatant were collected by a centrifugation at $257,000g_{max}$ for 90 min at 4ºC in a Ti70 rotor with a Beckman ultracentrifuge. Moreover, Morein et al. disclose that it is possible to dilute the supernatant from the low-speed centrifugation step with a buffer, mix it with Percoll and perform the density gradient centrifugation (see page 48; Preparation of Membrane Vesicles; 4th paragraph). Morein et al. disclose that the membrane pellet was suspended in a small volume buffer C, which included tris-HCL. The membrane mixture was mixed and then centrifuged (see page 48; Gradient Centrifugation; 1st paragraph). Morein et al. disclose that the supernatant from the low-speed centrifugation containing the membrane vesicles was directly diluted with buffer C, mixed with Percoll to a concentration of 16.2% by volume and centrifuged (see page 48; Gradient Centrifugation; 2nd paragraph).

Morein et al. do not specifically disclose that the outer membrane vesicle preparation is from *N. meningitidis* strain H44/76 or *N. gonorrhoeae* and over-expresses TbpA; they do not disclose that the process comprises sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition or that the pore size is about 0.2 µm.

Gorringe et al. disclose a process for the preparation of an outer membrane vesicle preparation; the method includes expressing recombinant neisserial TbpA (see page 5, lines 26 and 35). Gorringe et al. disclose that the invention provides a cell expressing Neisserial transferring binding protein (Tbp), wherein the Tbp can be extracted from the cell under mild conditions. Gorringe et al. disclose that the invention is an application for the overexpression of Tbps in organisms that are known to express Tbps. The invention is designed to use commensal Neisseria expressing an iron uptake protein from a pathogenic Neisseria, particularly one expressing TbpA (claim 1), such as *N. meningitidis* strain K454, which is a serogroup B bacterium (claim 11) (see page 4, lines 4, 5 and 12-14; page 7, lines 16-20). Gorringe et al. disclose that the Tbp is extracted by solubilising the membrane associated with Tbp in a non-ionic detergent

solution (see page 6, lines 1 and 2), thus meeting the limitation "in the absence of deoxycholate detergent". Moreover, Gorringe et al. disclose that crude membranes were prepared by disrupting cells with a bead-beater (the Examiner has interpreted this to meet the limitation of "wherein the bacterial membrane is disrupted substantially in the absence of any detergent). The cell suspension was transferred to a vessel half filled with 0.25-0.5mm diameter glass beads. The vessel was sealed and placed on to the bead-beating apparatus. The suspension was beaten for 15 seconds to disrupt the cells. Once the beads had settled the suspension was decanted off and centrifuged at 8000g for 30 min. The supernatant was discarded and the pellet containing crude membranes was resuspended in the original volume of 100 mM Tris-HCI buffer, pH 8,0, containing 0.5M NaCI. Once an even suspension was obtained an equal volume of Tris-HCI buffer, pH 8.0, containing 0.5M NaCI and 4% (v/v) Elugent ™ detergent was added. The suspension was incubated with gentle stirring at 4°C for 16 h. The suspension was then centrifuged at 39000g for 10 mi and the supernatant containing soluble rTbps was decanted off (see page 12, lines 25-37 and page 13, lines 1-2; extraction from membrane preparations). Gorringe et al. disclose that the composition can be included in vaccine compositions (see abstract).

van der Ley et al. disclose the use of *Neisseria meningitidis* strain H44/76 (claim 19) for the production of an outer membrane vesicle vaccine.

Rosenqvist et al. disclose a process for the production of outer membrane vesicle vaccines. Rosenqvist et al. disclose that sterile filtration of purified OMV is accomplished by using a series of three separate filters with decreasing pore sizes (claim 4) (see page 20, lines 1-12). Moreover, Rosenqvist et al. disclose the use of 0.2 µm filters (claim 8) (see page 20, line 30).

Morein et al. , Gorringe et al., van der Ley et al., and Rosenqvist et al. disclose analogous inventions related to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, it would have been prima facia obvious at the time the invention was made to use Neisseria bacterium that over-expresses TbpA because meningococcal infections are increasing and the meningococcal transferring receptor is a suitable vaccine component made up of transferring binding protein A (TbpA) and B

(TbpB), consequently producing outer membrane vesicle membranes that over-express TbpA provides an alternative and/or improved recombinant production of TbpA (see Gorringe et al.; page 1, lines 14-16 and page 2, lines 33-38).

It would have been prima facia obvious at the time the invention was made to use *N. meningitidis* strain H44/76, which is from serogroup B because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Moreover, it would have been obvious at the time the invention was made to perform sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition from step (f) because a smaller size filter, particularly a 0.2 µm filter yields vesicles with less rupture and damage (see Rosenqvist; page 21, line 1) and because the known technique was recognized as part of the ordinary capabilities of one skilled in the art.

It would have been expected, barring evidence to the contrary, that the strain together with the process steps would be effective for the manufacturing of an outer membrane vesicle. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396). By all comparative data the method of the prior art and the instantly claimed method absent evidence to the contrary are one in the same.

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
7/28/10

/Vanessa L. Ford/

Primary Examiner, Art Unit 1645